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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,326	08/28/2003	Keith A. Hruska	JJJ-P01-599	6882

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ROPES & GRAY LLP
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EXAMINER	
BORGEEST, CHRISTINA M	

ART UNIT	PAPER NUMBER
1649	

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11/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/650,326	Applicant(s) HRUSKA ET AL.	
	Examiner Christina Borgeest	Art Unit 1649	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10 October 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *56,69-76 and 78*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646

Continuation of 11. does NOT place the application in condition for allowance because: Applicants argue that their article published in 2000 (Hruska et al.) revealed that OP-1 and ACE inhibitors acted in a similar manner, namely, "the effects of ACE inhibition are mediated in part through inhibition of intrarenal paracrine functions of angiotensin II, which activates a damage cascade of cytokines and transcription factors in response to renal injury. OP-1 also inhibited the activation of the damage cascade as part of its mechanism of renal protection." Applicants go on to assert that it would be more likely and expected for two drugs to work at least in an additive and possibly synergistic manner if each works on a different target, but less likely for two drugs that work on the same target to exhibit additive or synergistic effect. Applicants argue that in fact it would be expected that the effect would be less than additive, as two drugs may interfere with each other or would overlap and be redundant. Finally, Applicants assert that enalapril is an example of the broad class of compounds that are all ACE inhibitors, thus is appropriate for the scope of the claim as recited. These arguments have been fully considered but are not found persuasive. First, it is not clear from the excerpt from Hruska et al. cited by Applicants mean that ACE inhibitors and OP-1 have the same molecular target. Hruska et al. reads "OP-1 also inhibited the activation of the damage cascade as part of its mechanism of renal protection", thus leaving open the possibility that it acts upon other targets as well. In addition, Applicants state at p. 7, 1st paragraph of their remarks that the mechanism of action by OP-1 is not well understood. Furthermore, according to Bell, (FEMS Microbiologty Letters. 2005; 253: 171-184) who wrote about synergism and antagonsim in antimalarial drugs:

"Therein lies another problem with many studies on antimalarial drug interactions, which is that synergism (or antagonism) can be taken to mean almost anything the investigator wants it to mean. For example, synergism between two agents is often taken as evidence that the relevant targets of the two agents form components of a common pathway. This may be true, but it has been argued that sequential inhibition of linear reactions in metabolic pathways by two or more inhibitors in the steady state alone cannot be synergistic (see discussion of antifolates below), so it is not necessarily so. Another liberty taken is to conclude from data showing antagonism between drugs A and B that the two drugs have a common target. One could also argue (as in example (i) above) that the same conclusion could be drawn from a synergistic interaction, or (returning to the case where A = B) from no interaction. Therefore, in the discussion of specific antimalarial drugs below, mechanistic inferences made from drug interaction data will be treated with caution unless there is a logical explanation and at least some supporting evidence for the effect.".

Although writing about antimalarial drugs, Bell's caution provides evidence that interpretation of the existence of synergism or antagonism between two drugs must be evaulated with caution and that although it may be so, it is not necessarily so that two drugs acting on the same target must necessarily be antagonistic. Finally, as stated above, the mechanism of action of OP-1 is not fully understood, thus it is premature to say that it has the same molecular target as ACE inhibitors.

Finally with regard to Applicants' arguments at p. 8 regarding Obviousness-Type Double Patenting, since the claims have not been indicated as allowable, the rejections (as set forth at pages 6-9 of the Final Office action mailed 11 June 2007) must be maintained.